30. (New) The protein of claim 7, wherein the amino acid sequence of said protein is identical to the amino acid sequence of RIP15 (SEQ ID NO: 3).

31. (New) The protein of claim 7, said protein interacting with a retinoid X receptor in an *in vivo* interaction trap assay.

REMARKS

The present claims recite retinoid X receptor-interacting proteins that have an amino acid sequence at least 85% identical to that of RIP15.

Claims 7, 10, 13-16, and 27 were examined in this case. The amino acid sequence of RIP15 (SEQ ID NO: 3) was determined to be free of the prior art. Claims 15, 16, and 27 stand objected to due to informalities. Claims 7, 10, 13-16, and 27 stand rejected under 35 U.S.C. § 101, § 112, first paragraph, § 102(b), and § 102(e). Each of these rejections is addressed as follows.

Support for the Amendments

Applicants have amended claims 7, 10, 13, 15, 16, and 27 and added new claims 28-31. Claims 7 and 10 now specify that the claimed RXR-interacting proteins have amino acid sequences that are at least 85% or 90% identical to the amino acid sequence of RIP-15 (SEQ ID NO: 3), respectively. Amended claim 27 recites RXR-interacting proteins produced by expression of a DNA encoding a protein having an amino acid sequence at least 85% identical to the amino acid sequence of RIP-15. New claims 28-30 recite RXR-interacting proteins having

amino acid sequences that are at least 95 or 100% identical to the amino acid sequence of RIP15. Support for these claim amendments and new claims can be found throughout the specification, for example, at page 6, line 27, through page 7, line 7; page 42; and Figure 5.

Applicants have also amended claims 15 and 16 to include the full names of β-RARE and EcRE, respectively. Support for these claim amendments can be found in the specification at page 21, lines 29-30, and at page 21, line 16.

New claim 31 also finds support throughout the application, for example, at pages 11-14, where *in vivo* interaction trap assays are described.

No new matter is added by any of the above amendments.

Objections to the Claims

Claim 15 and 16 stand objected to because the acronyms β-RARE and EcRE, respectively, are not identified with their full names. These objections have been met by the present amendments to claims 15 and 16, and may be withdrawn.

Claim 27 stands objected to because it is dependent upon a non-elected claim. This objection has been met by the present amendment to claim 27, and may be withdrawn.

Rejections under 35 U.S.C. § 101 and § 112, first paragraph

Claims 7, 10, 13-16, and 27 stand rejected under 35 U.S.C. § 101 and § 112, first paragraph, with the Examiner stating that the claimed invention is not supported by a substantial asserted utility or by a well established utility that would enable one skilled in the art to use the invention. For the following reasons, applicants respectively traverse these related rejections.

Claims 7, 10, 13-16, and 27 recite proteins that interact with the retinoid X receptor (RXR) and that have an amino acid sequence that is at least 85% identical to the amino acid sequence of RIP15 (SEQ ID NO: 3). Applicants discovered that RIP15 completely blocks RXR-dependent transcription of a reporter gene linked to a β-RARE element in a mammalian cell-based assay (page 24, lines 7 to 24, and Figure 9). As noted on page 40, lines 8 to 19, and page 42 of the specification, the ability of RIP15 to eliminate RXR-dependent activation of β-RARE linked genes strongly supports the specific utility of RIP15, analogs of RIP15, and fragments of RIP15 as therapeutics for the inhibition of RXR function in a subject.

Regarding the Office's argument that there is no connection between the properties of RIP15 and the treatment of disease, applicants respectfully assert that one skilled in the art would appreciate that the ability of RIP15 to inhibit RXR is indeed useful for the treatment of disease. As stated on page 2, lines 14-24, of the specification:

> members of the RXR family play important roles in several aspects of development and central nervous system differentiation as well as in adult physiology. Based on both their specific response to the 9-cis-RA metabolite and their heterodimerization with the RARs, it is clear that the RXRs play a central role in the broad regulatory effects of retinoids. Moreover, their heterodimeric interactions with other family members indicate that the RXRs also play a central role in response to thyroid hormone, vitamin D, and perhaps other compounds.

In particular, a skilled artisan would realize that inhibiting RXR function is desirable for the treatment of diseases associated with an elevated level of hormone (*e.g.*, thyroid hormone, retinoic acid, or vitamin D) or hormone-mediated activity. For example, hyperthyroidism is caused by the production of too much thyroid hormone, and thus hyperthyroidism can be treated by inhibiting the body's response to thyroid hormone. Because RXR is required for full hormone dependent transcriptional activity of the thyroid hormone receptor-RXR complex,

administration of RIP15 to a subject with hyperthyroidism should reduce the adverse effects cause by the excess thyroid hormone and the resulting excess thyroid hormone receptor activity (page 2, lines 4-6).

Additionally, RIP15 can be used in standard methods to identify compounds that increase or decrease its expression and therefore its interaction with RXR (see, for example, page 34, line 28 through page 35, line 12). One skilled in the art would appreciate that compounds that increase RIP15 expression are also useful for the treatment of diseases associated with an elevated level of hormone or hormone-mediated activity.

In addition to its therapeutic uses, RIP15 can be used for the generation of anti-RIP15 antibodies for the detection or monitoring of RXR-related diseases (see, for example, page 40, line 20 through page 41, line 12). For example, decreased levels of RIP15 are likely associated with increased risk or severity of RXR-associated diseases such as hyperthyroidism.

In response to the Examiner's assertion that RIP15 does not have a well established utility because its has no known ligand, applicants note that the inhibition of RXR activity by RIP15 is a well established utility that does not require the identification of a ligand for RIP15. In particular, RIP15 and polypeptides derived from RIP15 can be tested for their ability to inhibit RXR in the cell-based assay described in applicants' specification on pages 23 and 24 or in any animal model of disease without the use of a ligand for RIP15. A RIP15 ligand is also not needed to identify therapeutic compounds that modulate RIP15 expression or to generate anti-RIP15 antibodies for diagnostic applications.

Given the numerous uses of RIP15 based on applicants' demonstration of the ability of RIP15 to interact with and inhibit RXR, these related rejections under 35 U.S.C. § 101 and

§ 112, first paragraph should be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 7, 10, 13-15, and 27 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Leid *et al.* (Cell 68:377-395, 1992). Leid discloses the interaction of the human retinoic acid receptor with RXR. The present claims have been amended to specify that the recited proteins have an amino acid sequence that is at least 85% identical to that of RIP15 (SEQ ID NO: 3). Because Leid does not disclose such a protein, this rejection should be withdrawn.

Claims 7, 10, 13-14, 16, and 27 stand further rejected under 35 U.S.C. § 102(b) as being anticipated by Thomas *et al.* (Nature 362, 471-475, 1993). The Examiner also notes that Hogness *et al.* (U.S.P.N. 5,514,578) is cumulative to the Thomas reference. Both Thomas and Hogness disclose the Drosophila ecdysone receptor, which interacts with RXR. Because neither Thomas nor Hogness disclose a protein that has a sequence at least 85% identical to RIP15, this rejection should also be withdrawn.

Claims 7, 10, 13-16, and 27 stand further rejected under 35 U.S.C. § 102(e) as being anticipated by Liao *et al.* (U.S.P.N. 5,639,616). As stated in the attached Declaration of inventor Dr. David Moore, the RIP15 clone was isolated and sequenced prior to the November 10, 1993 filing date of Liao. Because the claimed invention was reduced to practice prior to the filing of Liao, Liao cannot constitute prior art to the present claims under 35 U.S.C. § 102(e). Accordingly, this rejection should also be withdrawn.

Potential Overlapping Subject Matter

For the record, applicants note that a PCT application (WO 95/13373, filed November 4, 1994) corresponding to the Liao U.S. patent has claims that recite nuclear receptor polypeptides (claims 17-22). While applicants are not aware of a related, pending U.S. patent application or issued U.S. patent that claims nuclear receptor polypeptides, applicants note that there is a possibility that a pending U.S. application claims overlapping subject matter with the present case.

Conclusion

Applicants submit that this case is now in condition for allowance, and such action is respectfully requested. A marked-up version indicating the amendments made to the claims, as required by 37 C.F.R. § 1.121(c)(1)(ii), is enclosed. Also enclosed is a petition to extend the period for replying for three months, to and including December 28, 2001, and a check for $460.00 for the required fee. A check for $36.00 in also enclosed for the excess claim fee.

If there are any other charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: December 25, 2001

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I hereby certify under 37 CFR 1.8(a) that this correspondence is being deposited with the United States Postal Service as **first class mail** with sufficient postage on the date indicated above and is addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231.

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Colleen Coyne — Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	David Moore et al.	Art Unit:	1646
Serial No.:	09/365,576	Examiner:	M. Pak
Filed:	August 2, 1999	Customer No.:	21559
Title:	RETINOID X RECEPTOR-INTERACTING POLYPEPTIDES AND RELATED MOLECULES AND METHODS		

Assistant Commissioner for Patents
Washington, D.C. 20231

Version with Markings to Show Changes Made

Marked-up versions of claims 7, 10, 13, 15, 16, and 27 and new claims 28-31 are presented below.

7. (Amended) A substantially pure RXR-interacting protein, comprising an amino acid sequence that is at least 85% identical to the amino acid sequence of RIP15 (SEQ ID NO: 3).

10. (Amended) The protein of claim 7, comprising an amino acid sequence that is at least 90% [substantially] identical to the amino acid sequence of RIP15 shown in Figure 5 (SEQ ID NO: 3).

13. (Amended) The protein of claim 7, wherein said protein [polypeptide] is derived from a mammal.

15. (Amended) The protein of claim 13, wherein said protein [polypeptide] binds a β-retinoic acid response element (β-RARE) [β-RARE site] in the presence of RXR.

16. (Amended) The protein of claim 13, wherein said protein [polypeptide] binds an ecdysone response element (EcRE) [EcRE site] in the presence of RXR.

27. (Amended) RXR-interacting protein produced by expression of a [the] purified DNA encoding a protein comprising an amino acid sequence that is at least 85% identical to the amino acid sequence of RIP15 (SEQ ID NO: 3) [of claim 17].

28. (New) The protein of claim 7, comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of RIP15 (SEQ ID NO: 3).

29. (New) The protein of claim 7, comprising an amino acid sequence that is identical to the amino acid sequence of RIP15 (SEQ ID NO: 3).

30. (New) The protein of claim 7, wherein the amino acid sequence of said protein is identical to the amino acid sequence of RIP15 (SEQ ID NO: 3).

31. (New) The protein of claim 7, said protein interacting with a retinoid X receptor in an *in vivo* interaction trap assay.